EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	32	FMO3 and trimethylamine and gene	US-PGPUB; USPAT; DERWENT	OR	ON	2006/09/21 13:05
L2	21	FMO3 and trimethylamine and gene and mutant	US-PGPUB; USPAT; DERWENT	OR	ON	2006/09/21 13:05
L3	32	FMO3 and trimethylamine and gene and (mutant mutation)	US-PGPUB; USPAT; DERWENT	OR	ON	2006/09/21 13:06
L4	32	FMO3 and trimethylamine and gene and (mutant or mutation)	US-PGPUB; USPAT; DERWENT	OR	ON	2006/09/21 13:10

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NEWS	5	MAY 11	KOREAPAT updates resume
NEWS	6	MAY 19	Derwent World Patents Index to be reloaded and enhanced
NEWS	7	MAY 30	IPC 8 Rolled-up Core codes added to CA/CAplus and USPATFULL/USPAT2
NEWS	8	MAY 30	The F-Term thesaurus is now available in CA/CAplus
NEWS	9	JUN 02	The first reclassification of IPC codes now complete in INPADOC
NEWS	10	JUN 26	TULSA/TULSA2 reloaded and enhanced with new search and and display fields
NEWS	11	JUN 28	Price changes in full-text patent databases EPFULL and PCTFULL
NEWS	12	JUl 11	CHEMSAFE reloaded and enhanced
NEWS	13	JUl 14	FSTA enhanced with Japanese patents
NEWS	14	JUl 19	Coverage of Research Disclosure reinstated in DWPI
NEWS	15	AUG 09	INSPEC enhanced with 1898-1968 archive
NEWS	16	AUG 28	ADISCTI Reloaded and Enhanced
NEWS	17	AUG 30	CA(SM)/CAplus(SM) Austrian patent law changes
NEWS	18	SEP 11	CA/CAplus enhanced with more pre-1907 records
NEWS	19	SEP 21	CA/CAplus fields enhanced with simultaneous left and right truncation

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=> s FMO3 and trimethylamine and gene and mutant
L1 28 FMO3 AND TRIMETHYLAMINE AND GENE AND MUTANT

=> d ibib abs l1 1-28

L1 ANSWER 1 OF 28 MEDLINE on STN
ACCESSION NUMBER: 2004641749 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15618671
TITLE: A mutation in the flavin-containing monooxygenase 3 gene and its effects on catalytic activity for N-oxidation of trimethylamine in vitro.
AUTHOR: Kubota Megumi; Nakamoto Yoko; Nakayama Kazuo; Ujjin Pailin; Satarug Soisungwan; Mushiroda Taisei; Yokoi Tsuyoshi; Funayama Masato; Kamataki Tetsuya
CORPORATE SOURCE: Laboratory of Drug Metabolism, Division of Pharmacobio-dynamics, Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo, Japan.
SOURCE: Drug metabolism and pharmacokinetics, (2002) Vol. 17, No. 3, pp. 207-13.
Journal code: 101164773. ISSN: 1347-4367.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: NONMEDLINE; PUBMED-NOT-MEDLINE
ENTRY MONTH: 200503
ENTRY DATE: Entered STN: 28 Dec 2004
Last Updated on STN: 30 Mar 2005
Entered Medline: 29 Mar 2005

AB To clarify the mutation of the flavin-containing monooxygenase (FMO) 3 gene causing fish-odor syndrome, we analyzed the FMO3 gene of a Thai subject who possibly suffered from fish-odor syndrome. A novel mutation, a single-base substitution from G to A at the position of 265 (G265A), was identified in exon 3. The mutation caused an amino acid substitution from valine to isoleucine at residue 58 (V58I). The mutated FMO3 protein with V58I exhibited the reduced trimethylamine N-oxidase activity when it was expressed in E.

coli. The V(max)/K(m) value for the activity of the mutant-type FMO3 was about 5 times lower than that for the wild-type FMO3.

L1 ANSWER 2 OF 28 MEDLINE on STN
ACCESSION NUMBER: 2003361161 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12893987
TITLE: Deleterious mutations in the flavin-containing monooxygenase 3 (FMO3) gene causing trimethylaminuria.
AUTHOR: Zhang Jun; Tran Quyen; Lattard Virginie; Cashman John R
CORPORATE SOURCE: Human Biomolecular Research Institute, 5310 Eastgate Mall, San Diego, CA 92121, USA.
CONTRACT NUMBER: DK/ES 59618 (NIDDK)
SOURCE: Pharmacogenetics, (2003 Aug) Vol. 13, No. 8, pp. 495-500. Journal code: 9211735. ISSN: 0960-314X.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200404
ENTRY DATE: Entered STN: 2 Aug 2003
Last Updated on STN: 23 Apr 2004
Entered Medline: 22 Apr 2004

AB The primary genetic form of trimethylaminuria (TMAU) is caused by inherited defects in the flavin-containing monooxygenase 3 (FMO3) gene. Defective FMO3 has a decreased ability to catalyze the N-oxygenation of the dietary-derived malodourous amine, trimethylamine. We report two novel deleterious mutations identified in two unrelated individuals affected by the disorder. Sequence analysis of the FMO3 coding exons amplified from genomic DNA revealed that the mutation from individual 1 was heterozygous for a G>A missense mutation in exon 2 of the FMO3 gene. The mutation changed a GAG encoding Glu at codon 32 to AAG encoding Lys. Wild-type and mutant E32K FMO3 were expressed in Escherichia coli as maltose binding-fusion proteins and assayed for their ability to catalyze oxygenation of various FMO3 substrates. The results showed that the E32K mutation abrogated the catalytic activity of the enzyme. Individual 2 was identified as heterozygous for the P153L mutation. In addition, individual 2 was also heterozygous for a novel single nucleotide deletion of A191 in exon 3 at codon 64. The deletion resulted in a frame shift and caused premature termination of the FMO3 gene immediately after codon 65. Family pedigree analysis revealed that the P153L and the deletion mutation were carried on different alleles for this individual. Therefore, both alleles of the FMO3 gene for individual 2 were affected by mutations abolishing the catalytic activity of the enzyme, explaining the severe TMAU condition. The two deleterious mutations reported herein were rare mutations with estimated allelic frequencies of less than 1%.

L1 ANSWER 3 OF 28 MEDLINE on STN
ACCESSION NUMBER: 2002704910 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12466292
TITLE: A nonsense mutation in the FMO3 gene underlies fishy off-flavor in cow's milk.
AUTHOR: Lunden Anne; Marklund Stefan; Gustafsson Victoria; Andersson Leif
CORPORATE SOURCE: Department of Animal Breeding and Genetics, Swedish University of Agricultural Sciences, Uppsala, Sweden.
SOURCE: Genome research, (2002 Dec) Vol. 12, No. 12, pp. 1885-8. Journal code: 9518021. ISSN: 1088-9051.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF488417; GENBANK-AF488418; GENBANK-AF488419; GENBANK-AF488420; GENBANK-AF488421; GENBANK-AF488422
ENTRY MONTH: 200301
ENTRY DATE: Entered STN: 17 Dec 2002
Last Updated on STN: 25 Jan 2003
Entered Medline: 24 Jan 2003

AB Fish-odor syndrome or Trimethylaminuria (OMIM #602079) in humans is an inborn error of metabolism associated with a characteristic fishy body odor due to elevated levels of trimethylamine (TMA) in body fluids. It is caused by loss-of-function mutations in FMO3 encoding flavin-containing mono-oxygenase 3. A fishy off-flavor is occasionally observed in cow's milk and it has been established recently that this phenotype is due to elevated TMA levels. Here, we report that fishy off-flavor in cow's milk is caused by a nonsense mutation (R238X) in the bovine FMO3 ortholog. RT-PCR analysis indicated that the mutant transcript is present in a very low amount. The mutation was found to be surprisingly common (q = 0.155) in one breed of cattle.

L1 ANSWER 4 OF 28 MEDLINE on STN
ACCESSION NUMBER: 2002456651 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12214664
TITLE: Genetic polymorphisms of flavin-containing monooxygenase (FMO).
AUTHOR: Krueger Sharon K; Williams David E; Yueh Mei-Fei; Martin Sarah R; Hines Ronald N; Raucy Judy L; Dolphin Colin T; Shephard Elizabeth A; Phillips Ian R
CORPORATE SOURCE: Department of Environmental and Molecular Toxicology and The Linus Pauling Institute, Oregon State University, Corvallis, USA.
CONTRACT NUMBER: HL38650 (NHLBI)
SOURCE: Drug metabolism reviews, (2002 Aug) Vol. 34, No. 3, pp. 523-32. Ref: 30
Journal code: 0322067. ISSN: 0360-2532.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200305
ENTRY DATE: Entered STN: 7 Sep 2002
Last Updated on STN: 15 May 2003
Entered Medline: 14 May 2003

AB Mammalian flavin-containing monooxygenase (FMO) exists as six gene families and metabolizes a plethora of drugs and xenobiotics. The major FMO in adult human liver, FMO3, is responsible for trimethylamine (TMA) N-oxygenation. A number of FMO3 mutant alleles have been described and associated with a disease termed trimethylaminuria (TMAU). The TMAU patient excretes large amounts of TMA in urine and sweat. A more recent ethnically related polymorphism in expression of the major FMO in lung, FMO2, has been described. All Caucasians and Asians genotyped to date are homozygous for a CAG --> TAG amber mutation resulting in a premature stop codon and a nonfunctional protein truncated at AA 472 (wildtype FMO2 is 535 AA). This allele has been designated hFMO2*2A. Twenty-six percent of individuals of African descent and 5% of Hispanics genotyped to date carry at least one allele coding for full-length FMO2 (hFMO2*1 allele). Preliminary evidence indicates that FMO2.1 is very active toward the S-oxygenation of low MW thioureas, including the lung toxicant ethylene thiourea. Polymorphic expression of functional FMO2 in the individuals of African and Hispanic descent may markedly influence drug metabolism and/or xenobiotic toxicity in the lung.

L1 ANSWER 5 OF 28 MEDLINE on STN

ACCESSION NUMBER: 2001017859 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10898113
TITLE: A novel mutation in the flavin-containing monooxygenase 3 gene, FM03, that causes fish-odour syndrome: activity of the mutant enzyme assessed by proton NMR spectroscopy.
AUTHOR: Murphy H C; Dolphin C T; Janmohamed A; Holmes H C; Michelakakis H; Shephard E A; Chalmers R A; Phillips I R; Iles R A
CORPORATE SOURCE: Cellular and Molecular Mechanisms Research Group, St Bartholomew's and The Royal London School of Medicine and Dentistry, Queen Mary and Westfield College, Whitechapel, London, UK.
SOURCE: Pharmacogenetics, (2000 Jul) Vol. 10, No. 5, pp. 439-51. Journal code: 9211735. ISSN: 0960-314X.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (CASE REPORTS) Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 22 Mar 2001
Entered Medline: 9 Nov 2000

AB We have previously shown that primary trimethylaminuria, or fish-odour syndrome, is caused by an inherited defect in the flavin-containing monooxygenase 3 (FMO3) catalysed N-oxidation of the dietary-derived malodorous amine, trimethylamine (TMA). We now report a novel causative mutation for the disorder identified in a young girl diagnosed by proton nuclear magnetic resonance (NMR) spectroscopy of her urine. Sequence analysis of genomic DNA amplified from the patient revealed that she was homozygous for a T to C missense mutation in exon 3 of the FMO3 gene. The mutation changes an ATG triplet, encoding methionine, at codon 82 to an ACG triplet, encoding threonine. A polymerase chain reaction/restriction enzyme-based assay was devised to genotype individuals for the FMO3Thr82 allele. Wild-type and mutant FMO3, heterologously expressed in a baculovirus-insect cell system, were assayed by ultraviolet spectrophotometry and NMR spectroscopy for their ability to catalyse the N-oxidation of TMA. The latter technique has the advantage of enabling the simultaneous, direct and semi-continuous measurement of both of the products, TMA N-oxide and NADP, and of one of the reactants, NADPH. Results obtained from both techniques demonstrate that the Met82Thr mutation abolishes the catalytic activity of the enzyme and thus represents the genetic basis of the disorder in this individual. The combination of NMR spectroscopy with gene sequence and expression technology provides a powerful means of determining genotype-phenotype relationships in trimethylaminuria.

L1 ANSWER 6 OF 28 JICST-EPlus COPYRIGHT 2006 JST on STN
ACCESSION NUMBER: 1020953023 JICST-EPlus
TITLE: A Mutation in the Flavin-containing Monooxygenase 3 Gene and its Effects on Catalytic Activity for N-oxidation of Trimethylamine In Vitro.
AUTHOR: KUBOTA M; NAKAMOTO Y; NAKAYAMA K; MUSHIRODA T; YOKOI T; KAMATAKI T
UJJIN P
SATARUG S
FUNAYAMA M
CORPORATE SOURCE: Hokkaido Univ., Sapporo, Jpn
Chulalongkorn Univ., Bangkok, Tha
Univ. Queensland, Brisbane, Aus
Sapporo Medical Univ., Sapporo, Jpn
SOURCE: Drug Metab Pharmacokinet, (2002) vol. 17, no. 3, pp.

207-213. Journal Code: X0758A (Fig. 2, Tbl. 3, Ref. 49)
ISSN: 0916-1139
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
LANGUAGE: English
STATUS: New
AB To clarify the mutation of the flavin-containing monooxygenase (FMO) 3 gene causing fish-odor syndrome, we analyzed the FMO3 gene of a Thai subject who possibly suffered from fish-odor syndrome. A novel mutation, a single-base substitution from G to A at the position of 265 (G265A), was identified in exon 3. The mutation caused an amino acid substitution from valine to isoleucine at residue 58 (V58I). The mutated FMO3 protein with V58I exhibited the reduced trimethylamine N-oxidase activity when it was expressed in E. coli. The Vmax/Km value for the activity of the mutant-type FMO3 was about 5 times lower than that for the wild-type FMO3. (author abst.)

L1 ANSWER 7 OF 28 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:500830 BIOSIS
DOCUMENT NUMBER: PREV200300502899
TITLE: Deleterious mutations in the flavin-containing monooxygenase 3 (FMO3) gene causing trimethylaminuria.
AUTHOR(S): Zhang, Jun; Tran, Quyen; Lattard, Virginie; Cashman, John R. [Reprint Author]
CORPORATE SOURCE: Human Biomolecular Research Institute, 5310 Eastgate Mall, San Diego, CA, 92121, USA
jcashman@hbri.org
SOURCE: Pharmacogenetics, (August 2003) Vol. 13, No. 8, pp. 495-500. print.
ISSN: 0960-314X.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 29 Oct 2003
Last Updated on STN: 29 Oct 2003
AB The primary genetic form of trimethylaminuria (TMAU) is caused by inherited defects in the flavin-containing monooxygenase 3 (FMO3) gene. Defective FMO3 has a decreased ability to catalyze the N-oxygenation of the dietary-derived malodourous amine, trimethylamine. We report two novel deleterious mutations identified in two unrelated individuals affected by the disorder. Sequence analysis of the FMO3 coding exons amplified from genomic DNA revealed that the mutation from individual 1 was heterozygous for a G>A missense mutation in exon 2 of the FMO3 gene . The mutation changed a GAG encoding Glu at codon 32 to AAG encoding Lys. Wild-type and mutant E32K FMO3 were expressed in Escherichia coli as maltose binding-fusion proteins and assayed for their ability to catalyze oxygenation of various FMO3 substrates. The results showed that the E32K mutation abrogated the catalytic activity of the enzyme. Individual 2 was identified as heterozygous for the P153L mutation. In addition, individual 2 was also heterozygous for a novel single nucleotide deletion of A191 in exon 3 at codon 64. The deletion resulted in a frame shift and caused premature termination of the FMO3 gene immediately after codon 65. Family pedigree analysis revealed that the P153L and the deletion mutation were carried on different alleles for this individual. Therefore, both alleles of the FMO3 gene for individual 2 were affected by mutations abolishing the catalytic activity of the enzyme, explaining the severe TMAU condition. The two deleterious mutations reported herein were rare mutations with estimated allelic frequencies of less than 1%.

L1 ANSWER 8 OF 28 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:91381 BIOSIS

DOCUMENT NUMBER: PREV200300091381
TITLE: A nonsense mutation in the FMO3 gene underlies fishy off-flavor in cow's milk.
AUTHOR(S): Lunden, Anne; Marklund, Stefan; Gustafsson, Victoria; Andersson, Leif [Reprint Author]
CORPORATE SOURCE: Department of Animal Breeding and Genetics, Swedish University of Agricultural Sciences, Uppsala, Sweden Leif.Andersson@bmc.uu.se
SOURCE: Genome Research, (December 2002) Vol. 12, No. 12, pp. 1885-1888. print.
ISSN: 1088-9051 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Feb 2003
Last Updated on STN: 12 Feb 2003

AB Fish-odor syndrome or Trimethylaminuria (OMIM 602079) in humans is an inborn error of metabolism associated with a characteristic fishy body odor due to elevated levels of trimethylamine (TMA) in body fluids. It is caused by loss-of-function mutations in FMO3 encoding flavin-containing mono-oxygenase 3. A fishy off-flavor is occasionally observed in cow's milk and it has been established recently that this phenotype is due to elevated TMA levels. Here, we report that fishy off-flavor in cow's milk is caused by a nonsense mutation (R238X) in the bovine FMO3 ortholog. RT-PCR analysis indicated that the mutant transcript is present in a very low amount. The mutation was found to be surprisingly common (q=0.155) in one breed of cattle.

L1 ANSWER 9 OF 28 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:333904 BIOSIS
DOCUMENT NUMBER: PREV200000333904
TITLE: A novel mutation in the flavin-containing monooxygenase 3 gene, FMO3, that causes fish-odour syndrome: Activity of the mutant enzyme assessed by proton NMR spectroscopy.
AUTHOR(S): Murphy, Helena C.; Dolphin, Colin T.; Janmohamed, Azara; Holmes, Heather C.; Michelakakis, Helen; Shephard, Elizabeth A.; Chalmers, Ronald A.; Phillips, Ian R.; Iles, Richard A. [Reprint author]
CORPORATE SOURCE: Medical Unit, Cellular and Molecular Mechanisms Research Group, St Bartholomew's and Royal London School of Medicine and Dentistry, Whitechapel, London, E1 1BB, UK
SOURCE: Pharmacogenetics, (July, 2000) Vol. 10, No. 5, pp. 439-451. print.
ISSN: 0960-314X.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Aug 2000
Last Updated on STN: 7 Jan 2002

AB We have previously shown that primary trimethylaminuria, or fish-odour syndrome, is caused by an inherited defect in the flavin-containing monooxygenase 3 (FMO3) catalysed N-oxidation of the dietary-derived malodorous amine, trimethylamine (TMA). We now report a novel causative mutation for the disorder identified in a young girl diagnosed by proton nuclear magnetic resonance (NMR) spectroscopy of her urine. Sequence analysis of genomic DNA amplified from the patient revealed that she was homozygous for a T to C missense mutation in exon 3 of the FMO3 gene. The mutation changes an ATG triplet, encoding methionine, at codon 82 to an ACG triplet, encoding threonine. A polymerase chain reaction/restriction enzyme-based assay was devised to genotype individuals for the FMO3Thr82 allele. Wild-type and mutant FMO3, heterologously expressed in a baculovirus-insect cell system, were assayed by ultraviolet spectrophotometry and NMR spectroscopy for their ability to catalyse the N-oxidation of TMA. The latter technique has the advantage of enabling

the simultaneous, direct and semi-continuous measurement of both of the products, TMA N-oxide and NADP, and of one of the reactants, NADPH. Results obtained from both techniques demonstrate that the Met82Thr mutation abolishes the catalytic activity of the enzyme and thus represents the genetic basis of the disorder in this individual. The combination of NMR spectroscopy with gene sequence and expression technology provides a powerful means of determining genotype-phenotype relationships in trimethylaminuria.

L1 ANSWER 10 OF 28 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:589059 CAPLUS
DOCUMENT NUMBER: 140:1315
TITLE: Deleterious mutations in the flavin-containing monooxygenase 3 (FMO3) gene causing trimethylaminuria
AUTHOR(S): Zhang, Jun; Tran, Quyen; Lattard, Virginie; Cashman, John R.
CORPORATE SOURCE: Human Biomolecular Research Institute, San Diego, CA, 92121, USA
SOURCE: Pharmacogenetics (2003), 13(8), 495-500
CODEN: PHMCEE; ISSN: 0960-314X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The primary genetic form of trimethylaminuria (TMAU) is caused by inherited defects in the flavin-containing monooxygenase 3 (FMO3) gene. Defective FMO3 has a decreased ability to catalyze the N-oxygenation of the dietary-derived malodorous amine, trimethylamine. The authors report two novel deleterious mutations identified in two unrelated individuals affected by the disorder. Sequence anal. of the FMO3 coding exons amplified from genomic DNA revealed that the mutation from individual 1 was heterozygous for a G>A missense mutation in exon 2 of the FMO3 gene. The mutation changed a GAG encoding Glu at codon 32 to AAG encoding Lys. Wild-type and mutant E32K FMO3 were expressed in Escherichia coli as maltose binding-fusion proteins and assayed for their ability to catalyze oxygenation of various FMO3 substrates. The results showed that the E32K mutation abrogated the catalytic activity of the enzyme. Individual 2 was identified as heterozygous for the P153L mutation. In addition, individual 2 was also heterozygous for a novel single nucleotide deletion of A191 in exon 3 at codon 64. The deletion resulted in a frame shift and caused premature termination of the FMO3 gene immediately after codon 65. Family pedigree anal. revealed that the P153L and the deletion mutation were carried on different alleles for this individual. Therefore, both alleles of the FMO3 gene for individual 2 were affected by mutations abolishing the catalytic activity of the enzyme, explaining the severe TMAU condition. The two deleterious mutations reported herein were rare mutations with estimated allelic frequencies of less than 1%.
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 11 OF 28 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:947980 CAPLUS
TITLE: A nonsense mutation in the FMO3 gene underlies fishy off-flavor in cow's milk
AUTHOR(S): Lunden, Anne; Marklund, Stefan; Gustafsson, Victoria; Andersson, Leif
CORPORATE SOURCE: Department of Animal Breeding and Genetics, Swedish University of Agricultural Sciences, Uppsala, Swed.
SOURCE: Genome Research (2002), 12(12), 1885-1888
CODEN: GEREFS; ISSN: 1088-9051
PUBLISHER: Cold Spring Harbor Laboratory Press

DOCUMENT TYPE: Journal; Letter
LANGUAGE: English
AB Fish-odor syndrome or Trimethylaminuria (OMIM #602079) in humans is an inborn error of metabolism associated with a characteristic fishy body odor due to elevated levels of trimethylamine (TMA) in body fluids. It is caused by loss-of-function mutations in FMO3 encoding flavin-containing mono-oxygenase 3. A fishy off-flavor is occasionally observed in cow's milk and it has been established recently that this phenotype is due to elevated TMA levels. Here, we report that fishy off-flavor in cow's milk is caused by a nonsense mutation (R238X) in the bovine FMO3 ortholog. RT-PCR anal. indicated that the mutant transcript is present in a very low amount The mutation was found to be surprisingly common (q = 0.155) in one breed of cattle.
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 12 OF 28 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:749673 CAPLUS
DOCUMENT NUMBER: 138:23159
TITLE: A mutation in the flavin-containing monooxygenase 3 gene and its effects on catalytic activity for N-oxidation of trimethylamine in vitro
AUTHOR(S): Kubota, Megumi; Nakamoto, Yoko; Nakayama, Kazuo; Ujjin, Pailin; Satarug, Soisungwan; Mushiroda, Taisei; Yokoi, Tsuyoshi; Funayama, Masato; Kamataki, Tetsuya
CORPORATE SOURCE: Laboratory of Drug Metabolism, Division of Pharmacobio-dynamics, Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo, Japan
SOURCE: Drug Metabolism and Pharmacokinetics (2002), 17(3), 207-213
CODEN: DMPRB8; ISSN: 1347-4367
PUBLISHER: Japanese Society for the Study of Xenobiotics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To clarify the mutation of the flavin-containing monooxygenase (FMO) 3 gene causing fish-odor syndrome, we analyzed the FMO3 gene of a Thai subject who possibly suffered from fish-odor syndrome. A novel mutation, a single-base substitution from G to A at the position of 265 (G265A), was identified in exon 3. The mutation caused an amino acid substitution from valine to isoleucine at residue 58 (V58I). The mutated FMO3 protein with V58I exhibited the reduced trimethylamine N-oxidase activity when it was expressed in E. coli. The Vmax/Km value for the activity of the mutant-type FMO3 was about 5 times lower than that for the wild-type FMO3.
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 13 OF 28 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:733723 CAPLUS
DOCUMENT NUMBER: 137:381528
TITLE: Genetic polymorphisms of flavin-containing monooxygenase (FMO)
AUTHOR(S): Krueger, Sharon K.; Williams, David E.; Yueh, Mei-Fei; Martin, Sarah R.; Hines, Ronald N.; Raucy, Judy L.; Dolphin, Colin T.; Shephard, Elizabeth A.; Phillips, Ian R.
CORPORATE SOURCE: Department of Environmental and Molecular Toxicology and The Linus Pauling Institute, Oregon State University, Corvallis, OR, USA
SOURCE: Drug Metabolism Reviews (2002), 34(3), 523-532
CODEN: DMTRAR; ISSN: 0360-2532

PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Mammalian flavin-containing monooxygenase (FMO) exists as six gene families and metabolizes a plethora of drugs and xenobiotics. The major FMO in adult human liver, FMO3, is responsible for trimethylamine (TMA) N-oxygenation. A number of FMO3 mutant alleles have been described and associated with a disease termed trimethylaminuria (TMAU). The TMAU patient excretes large amts. of TMA in urine and sweat. A more recent ethnically related polymorphism in expression of the major FMO in lung, FMO2, has been described. All Caucasians and Asians genotyped to date are homozygous for a CAG → TAG amber mutation resulting in a premature stop codon and a nonfunctional protein truncated at AA 472 (wild type FMO2 is 535 AA). This allele has been designated hFMO2*2A. Twenty-six percent of individuals of African descent and 5% of Hispanics genotyped to date carry at least one allele coding for full-length FMO2 (hFMO2*1 allele). Preliminary evidence indicates that FMO2.1 is very active toward the S-oxygenation of low MW thioureas, including the lung toxicant ethylene thiourea. Polymorphic expression of functional FMO2 in the individuals of African and Hispanic descent may markedly influence drug metabolism and/or xenobiotic toxicity in the lung. Supported by HL38650.
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 14 OF 28 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:528017 CAPLUS
DOCUMENT NUMBER: 134:16197
TITLE: A novel mutation in the flavin-containing monooxygenase 3 gene, FMO3, that causes fish-odor syndrome. Activity of the mutant enzyme assessed by proton NMR spectroscopy
AUTHOR(S): Murphy, Helena C.; Dolphin, Colin T.; Janmohamed, Azara; Holmes, Heather C.; Michelakakis, Helen; Shephard, Elizabeth A.; Chalmers, Ronald A.; Phillips, Ian R.; Iles, Richard A.
CORPORATE SOURCE: Medical Unit, Cellular and Molecular Mechanisms Research Group, St Bartholomew's and The Royal London School of Medicine and Dentistry, Queen Mary and Westfield College, London, UK
SOURCE: Pharmacogenetics (2000), 10(5), 439-451
CODEN: PHMCEE; ISSN: 0960-314X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors have previously shown that primary trimethylaminuria, or fish-odor syndrome, is caused by an inherited defect in the flavin-containing monooxygenase 3 (FMO3) catalyzed N-oxidation of the dietary-derived malodorous amine, trimethylamine (TMA). The authors now report a novel causative mutation for the disorder identified in a young girl diagnosed by proton NMR (NMR) spectroscopy of her urine. Sequence anal. of genomic DNA amplified from the patient revealed that she was homozygous for a T to C missense mutation in exon 3 of the FMO3 gene. The mutation changes an ATG triplet, encoding Met, at codon 82 to an ACG triplet, encoding Thr. A PCR/restriction enzyme-based assay was devised to genotype individuals for the FMO3Thr82 allele. Wild-type and mutant FMO3, heterologously expressed in a baculovirus-insect cell system, were assayed by UV spectrophotometry and NMR spectroscopy for their ability to catalyze the N-oxidation of TMA. The latter technique has the advantage of enabling the simultaneous, direct and semi-continuous measurement of both of the products, TMA N-oxide and NADP, and of 1 of the reactants, NADPH. Results obtained from both techniques demonstrate that the Met82Thr mutation abolishes the catalytic

activity of the enzyme and thus represents the genetic basis of the disorder in this individual. The combination of NMR spectroscopy with gene sequence and expression technol. provides a powerful means of determining genotype-phenotype relationships in trimethylaminuria.
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 15 OF 28 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:476355 CAPLUS
DOCUMENT NUMBER: 127:160127
TITLE: Human Flavin-Containing Monooxygenase Form 3: cDNA Expression of the Enzymes Containing Amino Acid Substitutions Observed in Individuals with Trimethylaminuria
AUTHOR(S): Cashman, John R.; Bi, Yi-An; Lin, Jing; Youil, Rima; Knight, Melanie; Forrest, Susan; Treacy, Eileen
CORPORATE SOURCE: Seattle Biomedical Research Institute, Seattle, WA, 98109, USA
SOURCE: Chemical Research in Toxicology (1997), 10(8), 837-841 CODEN: CRTOEC; ISSN: 0893-228X
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Trimethylaminuria is an autosomal recessive human disorder affecting a small part of the population as an inherited polymorphism. Individuals diagnosed with trimethylaminuria excrete relatively large amts. of trimethylamine in their urine, sweat, and breath, and this results in a fishy odor characteristic of trimethylamine. Activity of the human flavin-containing monooxygenase (FMO) has been proposed to be deficient in trimethylaminuria patients causing a decrease in the metabolism of trimethylamine that results in a fishy body odor. Cohorts of Australian, American, and British individuals suffering from trimethylaminuria have been identified. The human FMO3 cDNA was amplified from lymphocytes of affected patients. We report preliminary evidence of substitutions detected by screening of the cDNA and genomic DNA. The variant human FMO3 cDNA was constructed from wild type human FMO3 cDNA by site-directed mutagenesis as maltose-binding protein fusions. Five distinct human FMO3 mutants were expressed as fusion proteins in Escherichia coli and compared with wild type human FMO3 maltose-binding proteins (FMO3 -MBP) for the N-oxygenation of 10-[(N,N-dimethylamino)pentyl]-2-(trifluoromethyl)phenothiazine, tyramine, and trimethylamine. Human Lys158 FMO3-MBP and, to a greater extent, human Glu158 FMO3-MBP efficiently N-oxygenated the three amine substrates. Human Lys158 Ile66 FMO3-MBP, Glu158 Ile66 FMO3-MBP, Lys158 Leu153 FMO3-MBP, and Glu158 Leu153 FMO3-MBP were all constructed as mutants identified as possible FMO3 variants responsible for trimethylaminuria and were found to be inactive as N-oxygenases. The results suggest that mutations at codons 66 and 153 of FMO3 can cause trimethylaminuria in humans. We observed a common polymorphism of Lys to Glu at codon 158 of FMO3 that segregated with almost equal allele frequencies in a number of control Australian and North American samples studied. The Lys158 to Glu158 human FMO3 polymorphism does not decrease trimethylamine N-oxygenation for the cDNA-expressed enzyme and thus does not appear to be causative of trimethyaminuria. The data show that the functional activity of human FMO3 can be significantly altered by amino acid changes that have been observed in individuals with clin. diagnosed trimethylaminuria.
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 16 OF 28 LIFESCI COPYRIGHT 2006 CSA on STN
ACCESSION NUMBER: 2003:9159 LIFESCI

TITLE: A Nonsense Mutation in the FMO3 Gene Underlies Fishy Off-Flavor in Cow's Milk
AUTHOR: Lunden, A.; Marklund, S.; Gustafsson, V.; Andersson, L.
CORPORATE SOURCE: Department of Animal Breeding and Genetics, Swedish University of Agricultural Sciences, Uppsala, Sweden; E-mail: Leif.Andersson@bmc.uu.se
SOURCE: Genome Research [Genome Res.], (20021200) vol. 12, no. 12, pp. 1885-1888.
ISSN: 1054-9803.
DOCUMENT TYPE: Journal
FILE SEGMENT: G
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Fish-odor syndrome or Trimethylaminuria (OMIM #602079) in humans is an inborn error of metabolism associated with a characteristic fishy body odor due to elevated levels of trimethylamine (TMA) in body fluids. It is caused by loss-of-function mutations in FMO3 encoding flavin-containing mono-oxygenase 3. A fishy off-flavor is occasionally observed in cow's milk and it has been established recently that this phenotype is due to elevated TMA levels. Here, we report that fishy off-flavor in cow's milk is caused by a nonsense mutation (R238X) in the bovine FMO3 ortholog. RT-PCR analysis indicated that the mutant transcript is present in a very low amount. The mutation was found to be surprisingly common (q = 0.155) in one breed of cattle.

L1 ANSWER 17 OF 28 BIOTECHNO COPYRIGHT 2006 Elsevier Science B.V. on STN
ACCESSION NUMBER: 2003:37034591 BIOTECHNO
TITLE: Deleterious mutations in the flavin-containing monooxygenase 3 (FMO3) gene causing trimethylaminuria
AUTHOR: Zhang J.; Tran Q.; Lattard V.; Cashman J.R.
CORPORATE SOURCE: J.R. Cashman, Hum. Biomolecular Research Institute, 5310 Eastgate Mall, San Diego, CA 92121, United States.
E-mail: jcashman@hbri.org
SOURCE: Pharmacogenetics, (2003), 13/8 (495-500), 19 reference(s)
CODEN: PHMCEE ISSN: 0960-314X
DOCUMENT TYPE: Journal; Article
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English

AN 2003:37034591 BIOTECHNO

AB The primary genetic form of trimethylaminuria (TMAU) is caused by inherited defects in the flavin-containing monooxygenase 3 (FMO3) gene. Defective FMO3 has a decreased ability to catalyze the N-oxygenation of the dietary-derived malodourous amine, trimethylamine. We report two novel deleterious mutations identified in two unrelated individuals affected by the disorder. Sequence analysis of the FMO3 coding exons amplified from genomic DNA revealed that the mutation from individual 1 was heterozygous for a G>A missense mutation in exon 2 of the FMO3 gene. The mutation changed a GAG encoding Glu at codon 32 to AAG encoding Lys. Wild-type and mutant E32K FMO3 were expressed in Escherichia coli as maltose binding-fusion proteins and assayed for their ability to catalyze oxygenation of various FMO3 substrates. The results showed that the E32K mutation abrogated the catalytic activity of the enzyme. Individual 2 was identified as heterozygous for the P153L mutation. In addition, individual 2 was also heterozygous for a novel single nucleotide deletion of A191 in exon 3 at codon 64. The deletion resulted in a frame shift and caused premature termination of the FMO3 gene immediately after codon 65. Family pedigree analysis revealed that the P153L and the deletion mutation were carried on different alleles for this individual. Therefore, both alleles of the

FMO3 gene for individual 2 were affected by mutations abolishing the catalytic activity of the enzyme, explaining the severe TMAU condition. The two deleterious mutations reported herein were rare mutations with estimated allelic frequencies of less than 1%. .COPYRGT. 2003 Lippincott Williams & Wilkins.

L1 ANSWER 18 OF 28 BIOTECHNO COPYRIGHT 2006 Elsevier Science B.V. on STN
ACCESSION NUMBER: 2002:35469937 BIOTECHNO
TITLE: A nonsense mutation in the FMO3 gene underlies fishy off-flavor in cow's milk
AUTHOR: Lunden A.; Marklund S.; Gustafsson V.; Andersson L.
CORPORATE SOURCE: L. Andersson, Dept. of Animal Breeding/Genetics, Swedish Univ. Agricultural Sciences, Uppsala, Sweden. E-mail: Leif.Andersson@bmc.uu.se
SOURCE: Genome Research, (01 DEC 2002), 12/12 (1885-1888), 11 reference(s)
CODEN: GEREFS ISSN: 1088-9051
DOCUMENT TYPE: Journal; General Review
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2002:35469937 BIOTECHNO
AB Fish-odor syndrome or Trimethylaminuria (OMIM #602079) in humans is an inborn error of metabolism associated with a characteristic fishy body odor due to elevated levels of trimethylamine (TMA) in body fluids. It is caused by loss-of-function mutations in FMO3 encoding flavin-containing mono-oxygenase 3. A fishy off-flavor is occasionally observed in cow's milk and it has been established recently that this phenotype is due to elevated TMA levels. Here, we report that fishy off-flavor in cow's milk is caused by a nonsense mutation (R238X) in the bovine FMO3 ortholog. RT-PCR analysis indicated that the mutant transcript is present in a very low amount. The mutation was found to be surprisingly common (q = 0.155) in one breed of cattle.

L1 ANSWER 19 OF 28 BIOTECHNO COPYRIGHT 2006 Elsevier Science B.V. on STN
ACCESSION NUMBER: 2000:30433577 BIOTECHNO
TITLE: A novel mutation in the flavin-containing monooxygenase 3 gene, FMO3, that causes fish-odour syndrome: Activity of the mutant enzyme assessed by proton NMR spectroscopy
AUTHOR: Murphy H.C.; Dolphin C.T.; Janmohamed A.; Holmes H.C.; Michelakakis H.; Shephard E.A.; Chalmers R.A.; Phillips I.R.; Iles R.A.
CORPORATE SOURCE: R.A. Iles, Medical Unit, Cell. Mol. Mechanisms Research Group, Barts. Royal London Sch. Med. Dent., London E1 1BB, United Kingdom. E-mail: r.a.Iles@mds.qmw.ac.uk
SOURCE: Pharmacogenetics, (2000), 10/5 (439-451), 40 reference(s)
CODEN: PHMCEE ISSN: 0960-314X
DOCUMENT TYPE: Journal; Article
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2000:30433577 BIOTECHNO
AB We have previously shown that primary trimethylaminuria, or fish-odour syndrome, is caused by an inherited defect in the flavin-containing monooxygenase 3 (FMO3) catalysed N-oxidation of the dietary-derived malodorous amine, trimethylamine (TMA). We now report a novel causative mutation for the disorder identified in a young girl diagnosed by proton nuclear magnetic resonance (NMR) spectroscopy of her urine. Sequence analysis of genomic DNA amplified from the patient revealed that she was homozygous for a T to C missense mutation in exon 3

of the FMO3 gene. The mutation changes an ATG triplet, encoding methionine, at codon 82 to an ACG triplet, encoding threonine. A polymerase chain reaction/restriction enzyme-based assay was devised to genotype individuals for the FMO3Thr82 allele. Wild-type and mutant FMO3, heterologously expressed in a baculovirus-insect cell system, were assayed by ultraviolet spectrophotometry and NMR spectroscopy for their ability to catalyse the N-oxidation of TMA. The latter technique has the advantage of enabling the simultaneous, direct and semi-continuous measurement of both of the products, TMA N-oxide and NADP, and of one of the reactants, NADPH. Results obtained from both techniques demonstrate that the Met82Thr mutation abolishes the catalytic activity of the enzyme and thus represents the genetic basis of the disorder in this individual. The combination of NMR spectroscopy with gene sequence and expression technology provides a powerful means of determining genotype-phenotype relationships in trimethylaminuria. (C) 2000 Lippincott Williams and Wilkins.

L1 ANSWER 20 OF 28 BIOTECHNO COPYRIGHT 2006 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1997:27350041 BIOTECHNO
TITLE: Human flavin-containing monooxygenase form 3: cDNA expression of the enzymes containing amino acid substitutions observed in individuals with trimethylaminuria
AUTHOR: Cashman J.R.; Bi Y.-A.; Lin J.; Youil R.; Knight M.; Forrest S.; Treacy E.
CORPORATE SOURCE: J.R. Cashman, Seattle Biomedical Res. Institute, 4 Nickerson Street, Seattle, WA 98109, United States.
SOURCE: Chemical Research in Toxicology, (1997), 10/8 (837-841), 27 reference(s)
CODEN: CRTOEC ISSN: 0893-228X
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1997:27350041 BIOTECHNO
AB Trimethylaminuria is an autosomal recessive human disorder affecting a small part of the population as an inherited polymorphism. Individuals diagnosed with trimethylaminuria excrete relatively large amounts of trimethylamine in their urine, sweat, and breath, and this results in a fishy odor characteristic of trimethylamine. Activity of the human flavin- containing monooxygenase (FMO) has been proposed to be deficient in trimethylaminuria patients causing a decrease in the metabolism of trimethylamine that results in a fishy body odor. Cohorts of Australian, American, and British individuals suffering from trimethylaminuria have been identified. The human FMO3 cDNA was amplified from lymphocytes of affected patients. We report preliminary evidence of substitutions detected by screening of the cDNA and genomic DNA. The variant human FMO3 cDNA was constructed from wild type human FMO3 cDNA by site-directed mutagenesis as maltose-binding protein fusions. Five distinct human FMO3 mutants were expressed as fusion proteins in Escherichia coli and compared with wild type human FMO3 maltose-binding proteins (FMO3-MBP) for the N-oxygenation of 10- ¢(N,N-dimethylamino)pentyl!-2-(trifluoromethyl)phenothiazine, tyramine, and trimethylamine. Human Lys158 FMO3-MBP and, to a greater extent, human Glu158 FMO3-MBP efficiently N-oxygenated the three amine substrates. Human Lys158 Ile66 FMO3 -MBP, Glu158 Ile66 FMO3-MBP, Lys158 Leu153 FMO3-MBP, and Glu158 Leu153 FMO3-MBP were all constructed as mutants identified as possible FMO3 variants responsible for trimethylaminuria and were found to be inactive as N-oxygenases. The results suggest that mutations at codons 66 and 153 of FMO3 can cause trimethylaminuria in humans. We observed a common

polymorphism of Lys to Glu at codon 158 of FMO3 that segregated with almost equal allele frequencies in a number of control Australian and North American samples studied. The Lys158 to Glu158 human FMO3 polymorphism does not decrease trimethylamine N-oxygenation for the cDNA-expressed enzyme and thus does not appear to be causative of trimethyaminuria. The data show that the functional activity of human FMO3 can be significantly altered by amino acid changes that have been observed in individuals with clinically diagnosed trimethylaminuria.

L1 ANSWER 21 OF 28 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2005236406 EMBASE
TITLE: Mammalian flavin-containing monooxygenases: Structure/function, genetic polymorphisms and role in drug metabolism.
AUTHOR: Krueger S.K.; Williams D.E.
CORPORATE SOURCE: D.E. Williams, United States. david.williams@oregonstate.edu
SOURCE: Pharmacology and Therapeutics, (2005) Vol. 106, No. 3, pp. 357-387. .
Refs: 314
ISSN: 0163-7258 CODEN: PHTHDT
PUBLISHER IDENT.: S 0163-7258(05)00018-5
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 022 Human Genetics
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 7 Jul 2005
Last Updated on STN: 7 Jul 2005

AB Flavin-containing monooxygenase (FMO) oxygenates drugs and xenobiotics containing a "soft-nucleophile", usually nitrogen or sulfur. FMO, like cytochrome P450 (CYP), is a monooxygenase, utilizing the reducing equivalents of NADPH to reduce 1 atom of molecular oxygen to water, while the other atom is used to oxidize the substrate. FMO and CYP also exhibit similar tissue and cellular location, molecular weight, substrate specificity, and exist as multiple enzymes under developmental control. The human FMO functional gene family is much smaller (5 families each with a single member) than CYP. FMO does not require a reductase to transfer electrons from NADPH and the catalytic cycle of the 2 monooxygenases is strikingly different. Another distinction is the lack of induction of FMOs by xenobiotics. In general, CYP is the major contributor to oxidative xenobiotic metabolism. However, FMO activity may be of significance in a number of cases and should not be overlooked. FMO and CYP have overlapping substrate specificities, but often yield distinct metabolites with potentially significant toxicological/pharmacological consequences. The physiological function(s) of FMO are poorly understood. Three of the 5 expressed human FMO genes, FMO1, FMO2 and FMO3, exhibit genetic polymorphisms. The most studied of these is FMO3 (adult human liver) in which mutant alleles contribute to the disease known as trimethylaminuria. The consequences of these FMO genetic polymorphisms in drug metabolism and human health are areas of research requiring further exploration. .COPYRGT. 2005 Elsevier Inc. All rights reserved.

L1 ANSWER 22 OF 28 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2003345581 EMBASE
TITLE: Deleterious mutations in the flavin-containing monooxygenase 3 (FMO3) gene causing

trimethylaminuria.
AUTHOR: Zhang J.; Tran Q.; Lattard V.; Cashman J.R.
CORPORATE SOURCE: J.R. Cashman, Hum. Biomolecular Research Institute, 5310 Eastgate Mall, San Diego, CA 92121, United States. jcashman@hbri.org
SOURCE: Pharmacogenetics, (2003) Vol. 13, No. 8, pp. 495-500. .
Refs: 19
ISSN: 0960-314X CODEN: PHMCEE
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 11 Sep 2003
Last Updated on STN: 11 Sep 2003

AB The primary genetic form of trimethylaminuria (TMAU) is caused by inherited defects in the flavin-containing monooxygenase 3 (FMO3) gene. Defective FMO3 has a decreased ability to catalyze the N-oxygenation of the dietary-derived malodourous amine, trimethylamine. We report two novel deleterious mutations identified in two unrelated individuals affected by the disorder. Sequence analysis of the FMO3 coding exons amplified from genomic DNA revealed that the mutation from individual 1 was heterozygous for a G>A missense mutation in exon 2 of the FMO3 gene . The mutation changed a GAG encoding Glu at codon 32 to AAG encoding Lys. Wild-type and mutant E32K FMO3 were expressed in Escherichia coli as maltose binding-fusion proteins and assayed for their ability to catalyze oxygenation of various FMO3 substrates. The results showed that the E32K mutation abrogated the catalytic activity of the enzyme. Individual 2 was identified as heterozygous for the P153L mutation. In addition, individual 2 was also heterozygous for a novel single nucleotide deletion of A191 in exon 3 at codon 64. The deletion resulted in a frame shift and caused premature termination of the FMO3 gene immediately after codon 65. Family pedigree analysis revealed that the P153L and the deletion mutation were carried on different alleles for this individual. Therefore, both alleles of the FMO3 gene for individual 2 were affected by mutations abolishing the catalytic activity of the enzyme, explaining the severe TMAU condition. The two deleterious mutations reported herein were rare mutations with estimated allelic frequencies of less than 1%. .COPYRGT. 2003 Lippincott Williams & Wilkins.

L1 ANSWER 23 OF 28 EMBASE
ACCESSION NUMBER: 2002458219 EMBASE
TITLE: A nonsense mutation in the FMO3 gene underlies fishy off-flavor in cow's milk.
AUTHOR: Lunden A.; Marklund S.; Gustafsson V.; Andersson L.
CORPORATE SOURCE: L. Andersson, Dept. of Animal Breeding/Genetics, Swedish Univ. Agricultural Sciences, Uppsala, Sweden. Leif.Andersson@bmc.uu.se
SOURCE: Genome Research, (1 Dec 2002) Vol. 12, No. 12, pp. 1885-1888. .
Refs: 11
ISSN: 1088-9051 CODEN: GEREFS
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 3 Jan 2003
Last Updated on STN: 3 Jan 2003

AB Fish-odor syndrome or Trimethylaminuria (OMIM #602079) in humans is an

inborn error of metabolism associated with a characteristic fishy body odor due to elevated levels of trimethylamine (TMA) in body fluids. It is caused by loss-of-function mutations in FMO3 encoding flavin-containing mono-oxygenase 3. A fishy off-flavor is occasionally observed in cow's milk and it has been established recently that this phenotype is due to elevated TMA levels. Here, we report that fishy off-flavor in cow's milk is caused by a nonsense mutation (R238X) in the bovine FMO3 ortholog. RT-PCR analysis indicated that the mutant transcript is present in a very low amount. The mutation was found to be surprisingly common (q = 0.155) in one breed of cattle.

L1 ANSWER 24 OF 28 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2002324696 EMBASE
TITLE: Genetic polymorphisms of flavin-containing monooxygenase (FMO).
AUTHOR: Krueger S.K.; Williams D.E.; Yueh M.-F.; Martin S.R.; Hines R.N.; Raucy J.L.; Dolphin C.T.; Shephard E.A.; Phillips I.R.
CORPORATE SOURCE: D.E. Williams, Department of Molecular Toxicology, Linus Pauling Institute, Oregon State University, Corvallis, OR, United States. david.williams@orst.edu
SOURCE: Drug Metabolism Reviews, (2002) Vol. 34, No. 3, pp. 523-532. .
Refs: 30
ISSN: 0360-2532 CODEN: DMTRAR
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 3 Oct 2002
Last Updated on STN: 3 Oct 2002

AB Mammalian flavin-containing monooxygenase (FMO) exists as six gene families and metabolizes a plethora of drugs and xenobiotics. The major FMO in adult human liver, FMO3, is responsible for trimethylamine (TMA) N-oxygenation. A number of FMO3 mutant alleles have been described and associated with a disease termed trimethylaminuria (TMAU). The TMAU patient excretes large amounts of TMA in urine and sweat. A more recent ethnically related polymorphism in expression of the major FMO in lung, FMO2, has been described. All Caucasians and Asians genotyped to date are homozygous for a CAG → TAG amber mutation resulting in a premature stop codon and a nonfunctional protein truncated at AA 472 (wildtype FMO2 is 535 AA). This allele has been designated hFMO2*2A. Twenty-six percent of individuals of African descent and 5% of Hispanics genotyped to date carry at least one allele coding for full-length FMO2 (hFM02*1 allele). Preliminary evidence indicates that FMO2.1 is very active toward the S-oxygenation of low MW thioureas, including the lung toxicant ethylene thiourea. Polymorphic expression of functional FMO2 in the individuals of African and Hispanic descent may markedly influence drug metabolism and/or xenobiotic toxicity in the lung. Supported by HL38650.

L1 ANSWER 25 OF 28 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2000420052 EMBASE
TITLE: Correlation between FMO3 genotypes and FMO activity measured by using trimethylamine N-oxidation and ranitidine N-oxidation.
AUTHOR: Lee K.-H.; Song Ki Sung; Shin S.-G.; Cha Y.-N.
CORPORATE SOURCE: Dr. K.-H. Lee, Dept. of Pharmacology/Toxicology, College of Medicine, Inha University, Inchon, Korea, Republic of. youngnam@dragon.inha.ac.kr

SOURCE: Journal of Korean Society for Clinical Pharmacology and Therapeutics, (2000) Vol. 8, No. 1, pp. 44-59. .
Refs: 29
ISSN: 1225-5467 CODEN: LYHAEO
COUNTRY: Korea, Republic of
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English; Korean
ENTRY DATE: Entered STN: 14 Dec 2000
Last Updated on STN: 14 Dec 2000

AB Background: While trimethylamine (TMA) has been available for a non-invasive determination of flavin-containing monooxygenase 3 (FMO3) activity in man, it is contained in many foods and thus insensitive. We recently developed a non-invasive ranitidine N-oxidation test to determine the in vivo FMO activity. In this study, we compared the sensitivities of these two FMO phenotyping methods in reference to the FMO3 mutant geno-types by examining the functional effects of FMO3 E158K and E308G mutations on the rates of in vivo TMA N-oxidation and ranitidine N-oxidation by cross-over design. Methods: In 36 Korean healthy volunteers who were genotyped for the presence of K158 and G308 mutations in their FMO3 gene , FMO activities were determined by using ranitidine N-oxidation and TMA N-oxidation. Ratios of TMA N-oxide (TMAO) over total TMA (TTMA) in 24-hour urine and of ranitidine N-oxide versus ranitidine in 8-hour urine after an oral ingestion of 150 mg ranitidine were determined. Results: Ratios of TMAO/TTMA obtained in 13 subjects with homo- or heterozygous FMO3 K158 mutant alleles were not different from those of 23 subjects with wild type FMO3 E158 allele, and also, the ratios in 12 subjects with homo- or heterozygous FMO3 G308 mutant alleles were not different from those of 24 subjects with wild type FMO3 E308 allele. However, the ranitidine N-oxide/ranitidine ratios of 13 subjects with homo or heterozygous FMO3 K158 mutant alleles were significantly lower than those of the 23 subjects with FMO3 E158 wild type alleles, and also, the ratios of 12 subjects with FMO3 G308 mutant alleles were lower than those of the 23 subjects with wild type FMO3 E308 alleles. Conclusion: FMO activities determined by ranitidine N-oxidation, but not by TMA N-oxidation, were sensitively correlated with the common FMO3 E158K and E308G mutant genotypes in our Korean subjects.

L1 ANSWER 26 OF 28 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2000236346 EMBASE
TITLE: A novel mutation in the flavin-containing monooxygenase 3 gene, FMO3, that causes fish-odour syndrome: Activity of the mutant enzyme assessed by proton NMR spectroscopy.
AUTHOR: Murphy H.C.; Dolphin C.T.; Janmohamed A.; Holmes H.C.; Michelakakis H.; Shephard E.A.; Chalmers R.A.; Phillips I.R.; Iles R.A.
CORPORATE SOURCE: R.A. Iles, Medical Unit, Cell. Mol. Mechanisms Research Group, Barts. Royal London Sch. Med. Dent., London E1 1BB, United Kingdom. r.a.Iles@mds.qmw.ac.uk
SOURCE: Pharmacogenetics, (2000) Vol. 10, No. 5, pp. 439-451. .
Refs: 40
ISSN: 0960-314X CODEN: PHMCEE
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
029 Clinical Biochemistry

LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20 Jul 2000
Last Updated on STN: 20 Jul 2000

AB We have previously shown that primary trimethylaminuria, or fish-odour syndrome, is caused by an inherited defect in the flavin-containing monooxygenase 3 (FMO3) catalysed N-oxidation of the dietary-derived malodorous amine, trimethylamine (TMA). We now report a novel causative mutation for the disorder identified in a young girl diagnosed by proton nuclear magnetic resonance (NMR) spectroscopy of her urine. Sequence analysis of genomic DNA amplified from the patient revealed that she was homozygous for a T to C missense mutation in exon 3 of the FMO3 gene. The mutation changes an ATG triplet, encoding methionine, at codon 82 to an ACG triplet, encoding threonine. A polymerase chain reaction/restriction enzyme-based assay was devised to genotype individuals for the FMO3Thr82 allele. Wild-type and mutant FMO3, heterologously expressed in a baculovirus-insect cell system, were assayed by ultraviolet spectrophotometry and NMR spectroscopy for their ability to catalyse the N-oxidation of TMA. The latter technique has the advantage of enabling the simultaneous, direct and semi-continuous measurement of both of the products, TMA N-oxide and NADP, and of one of the reactants, NADPH. Results obtained from both techniques demonstrate that the Met82Thr mutation abolishes the catalytic activity of the enzyme and thus represents the genetic basis of the disorder in this individual. The combination of NMR spectroscopy with gene sequence and expression technology provides a powerful means of determining genotype-phenotype relationships in trimethylaminuria. (C) 2000 Lippincott Williams and Wilkins.

L1 ANSWER 27 OF 28 EMBASE

ACCESSION NUMBER: 1999251170 EMBASE
TITLE: The effect of arginine-428 mutation on modulation of activity of human liver flavin monooxygenase 3 (FMO3) by imipramine and chlorpromazine.
AUTHOR: Adali O.; Carver G.C.; Philpot R.M.
CORPORATE SOURCE: O. Adali, Department of Biology, Middle East Technical University, Ankara 06531, Turkey
SOURCE: Experimental and Toxicologic Pathology, (1999) Vol. 51, No. 4-5, pp. 271-276. .
Refs: 27
ISSN: 0940-2993 CODEN: ETPAEK
COUNTRY: Germany
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 2 Aug 1999
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AB This study was carried out to investigate the molecular basis for modulation of recombinant FMO3-catalyzed activity by the tricyclicantidepressants, imipramine and chlorpromazine. A mutant of human liver FMO3 (T428R) was formed by site-directed mutagenesis and characterized along with the native enzyme in order to elucidate a possible structure- function relationship. Functional properties of native and T428R human FMO3s were studied with methimazole as substrate. Both enzymes catalyzed the S- oxidation of methimazole with the same Km value. Imipramine modulated the activities of the native and T428R human FMO3s differently; the activity of the native FMO3 was increased at all concentrations, whereas the activity of the mutant enzyme was inhibited at concentrations above 300 μM.

Chlorpromazine activated the native enzyme at all concentrations of methimazole but activated the mutant enzyme only at high substrate concentrations. The direction (activation or inhibition) and extend of modulation of FMO3 activity is not only dependent on the concentration of the modulator, it is also dependent on the substrate concentration. This study confirms our previous findings with FMO1 that position 428 is important in the interaction of the FMO with modulators.

L1 ANSWER 28 OF 28 EMBASE

ACCESSION NUMBER: 97252473 EMBASE
DOCUMENT NUMBER: 1997252473
TITLE: Human flavin-containing monooxygenase form 3: cDNA expression of the enzymes containing amino acid substitutions observed in individuals with trimethylaminuria.
AUTHOR: Cashman J.R.; Bi Y.-A.; Lin J.; Youil R.; Knight M.; Forrest S.; Treacy E.
CORPORATE SOURCE: J.R. Cashman, Seattle Biomedical Res. Institute, 4 Nickerson Street, Seattle, WA 98109, United States
SOURCE: Chemical Research in Toxicology, (1997) Vol. 10, No. 8, pp. 837-841. .
Refs: 27
ISSN: 0893-228X CODEN: CRTOEC
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 007 Pediatrics and Pediatric Surgery
022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 18 Sep 1997
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AB Trimethylaminuria is an autosomal recessive human disorder affecting a small part of the population as an inherited polymorphism. Individuals diagnosed with trimethylaminuria excrete relatively large amounts of trimethylamine in their urine, sweat, and breath, and this results in a fishy odor characteristic of trimethylamine. Activity of the human flavin- containing monooxygenase (FMO) has been proposed to be deficient in trimethylaminuria patients causing a decrease in the metabolism of trimethylamine that results in a fishy body odor. Cohorts of Australian, American, and British individuals suffering from trimethylaminuria have been identified. The human FMO3 cDNA was amplified from lymphocytes of affected patients. We report preliminary evidence of substitutions detected by screening of the cDNA and genomic DNA. The variant human FMO3 cDNA was constructed from wild type human FMO3 cDNA by site-directed mutagenesis as maltose-binding protein fusions. Five distinct human FMO3 mutants were expressed as fusion proteins in Escherichia coli and compared with wild type human FMO3 maltose-binding proteins (FMO3 -MBP) for the N-oxygenation of 10- [(N,N-dimethylamino)pentyl]-2-(trifluoromethyl)phenothiazine, tyramine, and trimethylamine. Human Lys158 FMO3-MBP and, to a greater extent, human Glu158 FMO3-MBP efficiently N-oxygenated the three amine substrates. Human Lys158 Ile66 FMO3-MBP, Glu158 Ile66 FMO3-MBP, Lys158 Leu153 FMO3-MBP, and Glu158 Leu153 FMO3-MBP were all constructed as mutants identified as possible FMO3 variants responsible for trimethylaminuria and were found to be inactive as N-oxygenases. The results suggest that mutations at codons 66 and 153 of FMO3 can cause trimethylaminuria in humans. We observed a common polymorphism of Lys to Glu at codon 158 of FMO3 that segregated with almost equal allele frequencies in a number of control Australian and North American samples studied. The Lys158 to Glu158 human FMO3 polymorphism does not decrease

trimethylamine N-oxygenation for the cDNA-expressed enzyme and thus does not appear to be causative of trimethyaminuria. The data show that the functional activity of human FMO3 can be significantly altered by amino acid changes that have been observed in individuals with clinically diagnosed trimethylaminuria.